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ASYMMETRIC DEPROTONATION OF PROCHIRAL KETONES USING CHIRAL LITHIUM AMIDE BASES

Christian M. Cain, Richard P.C. Cousins, Greg Coumbarides and Nigel S. Simpkins*

Department of Chemistry, Queen Mary College, Mile End Road, London, E1 4NS.

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Abstract: A number of chiral secondary amines have been prepared and used as precursors to the corresponding chiral lithium amide bases. Treatment of either cis-2,6-dimethylcyclohexanone or 4-tert-butylcyclohexanone with a chiral lithium amide, followed by electrophilic quench, gives chiral products in up to 88% enantiomeric excess. The results with 4-tert-butylcyclohexanone are in disagreement with an earlier literature report, giving products of lower enantiomeric excess but higher optical rotation.

We recently reported the first examples of the use of chiral lithium amide bases in asymmetric deprotonations of symmetrically substituted ketones[1] Since that time a number of other reports have focussed attention on this new method for asymmetric synthesis, and we now describe further details of our reactions which produce chiral products in up to 88% enantiomeric excess (ee).[2]

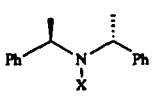
At the outset of this work very little chemistry had been carried out using chiral lithium amides. Chiral lithium amides had been generated from optically active secondary amines by Whitesell, and used to convert epoxides to chiral allylic alcohols, in modest ee.[3] One report by Hogeveen concerned partial deracemisation of a racemic ketone by means of chiral base.[4] Our plan was to convert prochiral ketones to chiral products via kinetically controlled asymmetric deprotonation using this type of strong base. Chiral lithium amides derived from amines having C_2 symmetry appeared very attractive for this chemistry, and so amines (1a) and (2), used previously by Whitesell and Hogeveen, respectively, looked to be likely candidates. Pyrrolidine (2), however, required a multistep preparation (including a resolution),[5] and so we decided to concentrate initially on the preparations of simpler amines (including (1a) starting with (R)- or (S)-1-phenylethylamine.

Results and Discussion

Either (R)- or (S)-1-phenylethylamine could be converted to the amines (3a) or (4a), respectively, by reaction with benzaldehyde and $NaBH_3CN$ in MeOH at room temperature. After workup, the secondary amines were purified by

* Author to whom correspondence should be addressed.
Present address, Department of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD.

distillation and/or crystallisation of the HCl salts. This procedure proved more convenient than an alternative we had employed earlier, which consisted of forming the benzamide (5), and subsequent reduction using $LiAlH_4$. The one-pot reductive amination procedure using $NaBH_3CN$ was also used to prepare (6a), $[\alpha]_D^{21}$ +61.9°. In the case of amine (1a), we employed the method of Overburger et al,[6] which involved isolation of the intermediate imine (7). Thus, (R)-1-phenylethylamine was reacted with acetophenone and p-toluene-sulphonic acid (PTSA) in benzene under reflux (3 days) and the desired imine was isolated after workup and distillation (b.p. 123-125°C, 0.6 mm Hg). Reduction in this case involved hydrogenation at atmospheric pressure using THF as solvent and 10% Pd/C as catalyst. The reported purification of the resultant amine (1a) requires recrystallisation of the HCl salt, followed by amine regeneration using KOH(aq) and distillation. We were very concerned when, after recrystallisation, the optical rotation of our HCl salt of (1a) matched the literature value ($[\alpha]_D$+70°, lit.$[\alpha]_D$ -71° for (S,S)-isomer), but our regenerated amine had a much lower optical rotation than that reported ($[\alpha]_D$ +167.0°, lit.$[\alpha]_D$ -196.3°). However, we were pleased to find that later reports by Hogeveen ($[\alpha]_D$ -157°)[7] and Marshall ($[\alpha]_D$ +167.6°)[8] agreed reasonably well with our result. Marshall has shown that his material is at least 95% optically pure.



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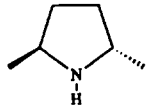

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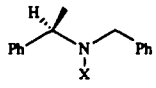

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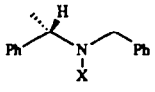

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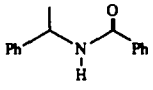

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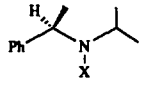

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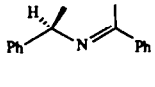
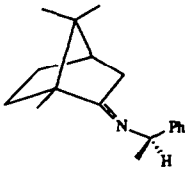


(7)

We have also prepared a number of bases via reductive amination starting with camphor. Here we were unable to use the one-pot procedure to combine camphor with a primary amine to give the desired product. Indeed we found that attempted reaction of camphor with primary amines in benzene or toluene under Dean-Stark conditions was unsuccessful, and more forcing conditions were required. Thus, heating camphor and (R)-1-phenylethylamine together without solvent at 120°C (3 days) in the presence of molecular sieves and small amounts of camphorsulphonic acid (CSA) gave the desired imine (8), b.p.

120°C, 0.15 mm Hg. The imine was next smoothly reduced using $NaBH_3CN$ in MeOH at pH 6-7 to give the amine (9a) in about 40-50% overall yield. Higher yields of amine (60-70%) were obtained if purification of the intermediate imine was omitted. Several other amines were prepared similarly, including the important base (10a) derived from camphor and aniline. Other amines prepared include the camphor-derived compounds (11) and (12),[9] and also amines (13)[10] and (14)[11] prepared by the published procedures.



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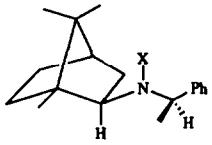

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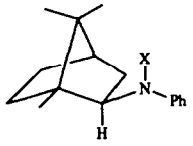
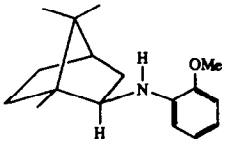
(9b) X=Li



(10a) X=H
(10b) X=Li



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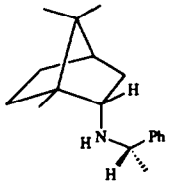

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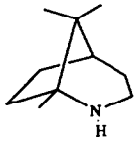

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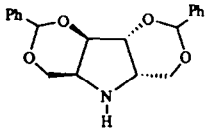
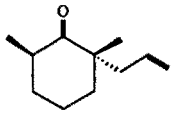
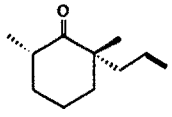


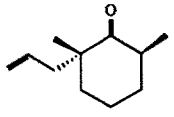
(14)

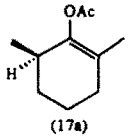
In our first attempt at asymmetric deprotonation we utilised chiral lithium amide (3b), and used as the carbonyl substrate cis-2,6-dimethylcyclohexanone. Thus a solution of (3a) in THF at -10°C was treated with $^{n}BuLi$ and stirred for 1 h before cooling to -78°C. The cis-2,6-dimethylcyclohexanone was then added dropwise as a solution in THF, and the reaction maintained at -78°C for 3 h before addition of excess allyl bromide. The mixture was then allowed to warm slowly to 0°C, and when reaction was complete (TLC, 4-6 h) it was poured into 2N HCl (aq) and the product extracted into ether. Washing the ether layer with 2N HCl served to remove the amine (3a), leaving the crude mixture of volatile allylated products (15), in which (15a) was the major diastereomer.[12] After chromatography, ketone (15a) was isolated as a mobile colourless oil ($[\alpha]_D$ -26°) in 50-65% yield. Yields of this ketone were somewhat variable since losses occurred due to its volatility. The ee of (15a) was judged from nmr experiments using the chiral shift reagent $[Eu(hfc)_3]$[13] to be ca.25%. This initial experiment was repeated using the enantiomeric lithium amide base (4b) to give the enantiomeric ketone (16), again in 25% ee. At this point we repeated the reactions with some minor modifications to the experimental conditions, in an attempt to improve the enantioselectivity. The use of dimethoxyethane (DME), or THF containing hexamethylphosphoric triamide (HMPA)(ca. 10% v/v) as

solvent for the deprotonation gave lower ee. The use of ether as solvent in this reaction gave unsatisfactory results due to poor solubility of the chiral base at low temperature. Stirring the reaction mixture longer at -78°C before addition of alkyl bromide, or starting the deprotonation at lower temperature (-110°C) did not affect the ee significantly. The alkylation reaction (originally carried out by Smith at room temperature overnight)[12] was somewhat sluggish, and we were concerned that allowing the mixture to stand at 0°C could have resulted in some degree of enolate equilibration, and hence racemisation. The reaction was found to proceed rather more smoothly if the deprotonation step was conducted as before in THF, but with HMPA (ca. 10% v/v) added just prior to the addition of allyl bromide. Under these conditions reaction was complete upon slow warming of the mixture to -10°C, with the product being obtained in similar yield and optical purity as before. Conceivably the use of HMPA in the reaction could also have resulted in enolate equilibration. Thus we carried out an alternative enolate quench using Ac_2O. This reaction occurred rapidly in the absence of HMPA on warming the reaction mixture to about -40°C, to form the enol acetate (17a) in 70-80% yield, again in 25% ee. These chiral enol acetates proved most convenient in determining the enantiomeric excess in such deprotonations, since only one chiral centre is present (hence no diastereomers to separate), and because splitting of the $OCOCH_3$ ^1H nmr signal in the presence of $[Eu(hfc)_3]$ gave a clear estimate of the ee.

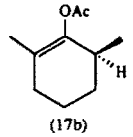

(15a)


(15b)


(16)



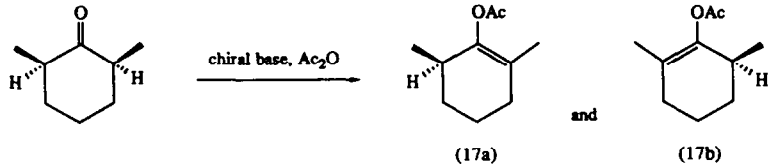
(17a)



(17b)

Further deprotonation experiments using other chiral amines as sources of the lithium amide were next carried out. Unexpectedly the first reaction using base (9b) caused problems due to ^nBuLi attacking the starting ketone. Subsequent experiments lead us to use longer periods (2 h) at room temperature to generate the lithium amide from this rather sterically hindered amine.[14] With this problem solved the deprotonation reactions again worked smoothly, provided that the deprotonation times were also extended (6-8 h). Table 1 indicates the ee and absolute stereochemistry of the enol acetates formed using a variety of chiral lithium amides in the same way.

Most notably the camphor-derived bases (9b) and (10b) gave enantiocomplementary results, with (10b) giving the highest ee of 74%. Asymmetric allylation reactions were also conducted using cis-2,6-dimethylcyclohexanone and the lithium amide bases (9b) or (10b). Allylated products



(17a) (17b)

base	yield	ee[a]	R or S
1b	71	43	R
3b	75	29	R
6b	71	32	S
9b	65	65	S
10b	68	74	R
12	76	5[b]	R
13	70	14[b]	R
14	28	8[b]	R

(a) Determined by the use of $Eu(hfc)_3$, except for (b) - approximate values by comparison of optical data.

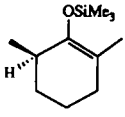
Table 1

were obtained with similar ee's to the corresponding enol acetates obtained previously, although the ee using base (10b) was slightly lower; 68% as opposed to 74% for the enol acetate.

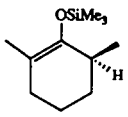
Significantly, when trans-2,6-dimethylcyclohexanone was reacted under identical conditions (using base (3b)) to the cis-isomer, racemic product was formed. This result was expected, since in the trans-ketone the two removable hydrogens are homotopic and therefore identical to a chiral base. We have not yet investigated incomplete deprotonations of the trans-ketone, which could potentially result in kinetic resolution; however, studies in this area are planned in the near future. The trans-ketone giving racemic product was a result which strongly supported our proposed mechanism for the asymmetric induction, which involves kinetically controlled asymmetric deprotonation. As a further check against possible effects due to enolate association with the chiral secondary amine, we conducted a further experiment. The asymmetric allylation of the cis-ketone using the chiral base (3b) was carried out as described above, but with addition of the free amine (4a) (1 equiv.) prior to addition of allyl bromide. The chiral product (15a) was obtained with similar ee to the earlier experiments. Any chelation effects due to (3a) should have been cancelled out by the addition of the enantiomeric amine (4a), providing further evidence for the formation of a chiral enolate in the deprotonation

step, the ee of which is relatively unaffected by subsequent additives.

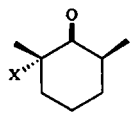
The preparation of the silyl enol ethers (18) was also straightforward, using (9b) or (10b) as before, and then quenching the reaction with Me_3SiCl, or a mixture of Me_3SiCl and Et_3N. These products were either used directly, or purified by chromatography on florisil. Subsequent reactions of (18a) or (18b) gave chiral ketone products. For example reaction of (18b) with mCPBA in petroleum ether gave the hydroxy ketone (19) ($[\alpha]_D$ +25.5°) in 61% yield and as a single diastereomer. Similarly, reaction with N-bromosuccinimide (NBS) in CH_2Cl_2 gave the bromoketone (20), although in rather poor (40%) yield. Finally the C-acylated product (21) was obtained in 33% yield by reaction with CH_3COCl and $SnCl_4$. The ee of the bromoketone (20) was again determined using nmr shift reagents and found to be similar to the ee of the corresponding enol acetate (17b). The ee of (19) was also later confirmed using Mosher derivatives.



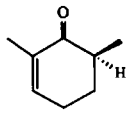
(18a)



(18b)



(19) X=OH (20) X=Br
(21) X=$COCH_3$ (22) X=SePh



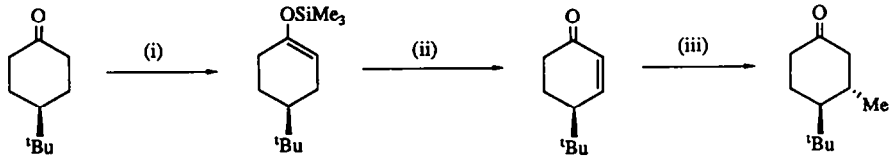
(23)

Our assignment of the absolute stereochemistry of these products was based on the application of the ketone octant rule to the CD curve obtained for (15a).[15] Confirmation of this assignment later came from two other sources. Firstly, silyl enol ether (18b) was converted using PhSeCl to the selenoketone (22), which was then exposed to H_2O_2 to effect selenoxide formation/syn-elimination to give the known enone (23) in 78% yield.[16] The sign of the optical rotation of this product ($[\alpha]_D$ -58.2°, lit.[16] $[\alpha]_{578}$ -82°) was consistent with our earlier assignment of absolute stereochemistry. Furthermore, the magnitude of the rotation was consistent with our expectation of ca. 70% optical purity. We were also able to convert the hydroxyketone (19) to two simple natural products of known absolute configuration, and again the assignments matched.[17]

A feature of this chemistry which is particularly convenient is the easy recoverability of most of the chiral amines. We have recovered amines such as (9a) by basification of the HCl (aq.) washings carried out on workup, in ca. 90% yield after distillation and with no change in optical rotation. However, some amines do suffer degradation in the reaction. For example the benzylidene protection on pyrrolidine (14) proved labile to acidic workup, whilst the camphor base (10a) is recovered with other minor, as yet unidentified amine impurities (presumably due to attack by ^nBuLi).

We next turned our attention to the possibility of using a 4-substituted cyclohexanone system in the asymmetric deprotonation process. In preliminary

reactions using 4-tert-butylcyclohexanone (24) we formed optically active enol acetate products, but were unable to determine their ee using chiral shift reagents. At this time a report from the research group of Koga described his independent studies concerning asymmetric deprotonation of 4-substituted cyclohexanones, including 4-tert-butylcyclohexanone.[18] One result involved the formation of silyl enol ether (25) in 84% ee using base (6b). This reaction was done by premixing the chiral base and Me_3SiCl at low temperature before addition of the ketone.[19] This internal quench method gave very good yields and ee's of up to 97%, vide infra. The absolute configuration and optical purity of (25) obtained in this way were established by converting it (material of 56% ee was used) to the known ketone (27) via enone (26), Scheme 1.

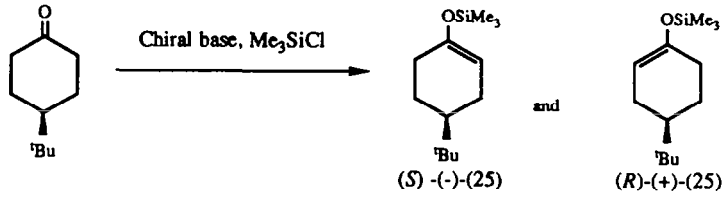


(24) (25) (26) (27)

Reagents (i) (6b), Me_3SiCl (ii) $Pd(OAc)_2$, diallylcarbonate, CH_3CN (iii) Me_2CuLi

Scheme 1

We also carried out the preparation of (25) using the same conditions as Koga and found that with lithium amide (6b) the best optical rotation we could achieve was $[\alpha]_D$ -51° (-90°C rather than -78°C). We could not compare this figure directly with the Koga result since he quoted $[\alpha]_{365}$ -181°. We therefore decided to repeat the conversion of (25) through to (27) which is reported to show $[\alpha]_D$ +247.8°.[20] Initially we used the same method as Koga to convert our silyl enol ether (25) to the enone (26). Thus (25) ($[\alpha]_D$ -36.2°) was heated under reflux in CH_3CN containing $Pd(OAc)_2$ and diallylcarbonate to give enone (26) ($[\alpha]_D$ -28.1°) in 86% yield.[21] Subsequent reaction with Me_2CuLi in ether at -78°C then gave ketone (27) in 65% yield having $[\alpha]_D$ -111.5°. This corresponds to only 45% optical purity compared to the 84% quoted by Koga. A different batch of silyl enol ether (25) ($[\alpha]_D$-42.9°) was also converted to ketone (27) but this time we used the selenation-syn-elimination procedure we employed earlier to obtain enone (23). Again a low optical purity was obtained: 51%. We eventually obtained $[\alpha]_{365}$ values for our silyl enol ether (23),[15] and found that they were considerably lower than those of Koga for this particular base, i.e. $[\alpha]_{365}$ -161° (optimum) compared to -181°. We next decided to survey some other bases for the enantioselective formation of silyl enol ether (25). Our results are shown in Table 2.

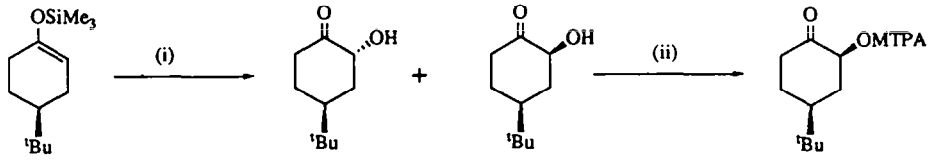


base	temp °C	yield	$[\alpha]_D$	$[\alpha]_{365}$	ee[c]
1b	-78	73	-54.4	-171.5	(70)
	-90	66	-69.2	-218.6	88[a]
3b	-78	71	-42.9	-133.9	51[b]
6b	-78	82	-44.9	-	(59)
	-78	80	-36.2	-116	45[b]
	-90	81	-51.0	-	(66)
9b	-78	80	-16.1	-	(21)
10b	-78	75	-23.5	67.9	(31)

a - by conversion to (29)
b - by conversion to (27)
c - approximate values in brackets calculated using optical data

Table 2

As can be seen, our camphor-derived chiral lithium amides proved rather disappointing, whilst base (1b) gave product having very high optical rotations of $[\alpha]_D$ -69.2° and $[\alpha]_{365}$ -218.6°. The optical purity of this product, by extrapolation of the literature values mentioned above, would be > 100%![22] We decided to check this result by converting the silyl enol ether to the α-hydroxyketones (28) ((28a):(28b) ca.10:1) using mCPBA. Compound (28a) was then completely converted to its (R)-methoxytrifluoromethylphenylacetyl (MTPA) ester (> 95% yield) and the ^1H nmr spectrum compared with that of the MTPA ester prepared using racemic hydroxyketone (28a), Scheme 2.[23]

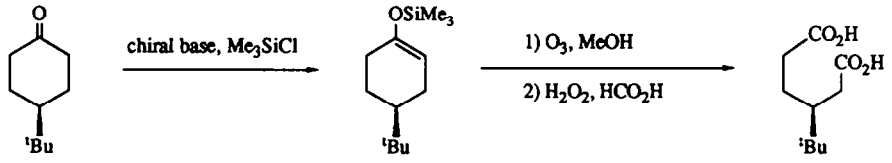


(i) mCPBA (ii) MTPACl

Scheme 2

This analysis clearly showed a de of 88%. Thus the silyl enol ether (25) having $[\alpha]_D$ -69.2° would have an ee of 88%, assuming no loss of optical purity in the reaction with mCPBA. This result is consistent with our earlier preparation of ketone (27), in which starting silyl enol ether $[\alpha]_D$ -36.2° gave the final ketone of 45% optical purity.

A further check on the enantiomeric purity of the silyl enol ether (25) was carried out by converting it to the known diacid (30)[24] ($[\alpha]_D$ +17.2° c 1.0 acetone) as in Scheme 3.



(24) (25) (30)

yield	$[\alpha]_D$ ($CHCl_3$)	ee[a]	yield	$[\alpha]_D$ (acetone)	ee[b]
84	-12.7	16	62	+ 2.4	16
44	-48.8	63	60	+11.4	66
89	-56.9	73	58	+13.2	76
70	-67.2	86	60	+15.2	88

a - by comparison with material of $[\alpha]_D$ -69.2° shown to be 88% ee

b - by comparison with the literature rotation of the diacid (30)

Scheme 3

As can be seen the optical purities of the product diacid match well with that anticipated from our earlier results.

The differences between some of our rotation values and those reported previously (e.g. using base 6b) can be explained by solvent effects,[22] and possibly minor variations in reaction conditions. However, our results indicate that there is an error in the estimation of ee in the previous work, which relies solely on one correlation with a literature compound. Our analysis relies not only on independent correlation to compounds (27) and (30) (at several different ee levels) but also by direct determination using the MTPA derivative (29). The previous results for this compound therefore represent lower levels of asymmetric induction than at first thought.

We have subsequently applied the Me_3SiCl *in situ* quench technique to the *cis*-2,6-dimethylcyclohexanone system. To our surprise, using base (9b) under the conditions used for 4-*tert*-butylcyclohexanone, which employed only a 10 minute reaction time, we observed virtually no reaction. However on extending the reaction time to 14 hours (coldplate overnight -78°C to -40°C)

we were able to obtain a 30% yield of silyl enol ether (18b). Pleasingly, this material was shown to have an ee of 83% by conversion to the Mosher (MTPA) ester (97% yield, 83% de) of the corresponding alcohol (19). Thus a significant increase in ee (68% to 83%) was observed by changing to the *in situ* technique. Unfortunately we have been unable to increase the yield in this process, and the long reaction times (which we were hoping would not be needed by comparison with the very fast reactions with 4-*tert*-butylcyclohexanone) are inconvenient unless a coldplate is used. The problem seems to be that *cis*-2,6-dimethylcyclohexanone is deprotonated only *very* slowly at the low temperatures required for good enantioselectivity. In the *in situ* quench reactions it is more than likely that the Me_3SiCl and chiral lithium amide are not completely compatible over such long periods, thus giving lower yields. We also used the chiral bases (10b) and (1b) to deprotonate *cis*-2,6- dimethylcyclohexanone using the *in situ* quench technique. Improved enantioselectivities were again observed (with (10b) 77% ee, and with (1b) 53% ee), but yields remained at *ca*. 30%.

Conclusion

The use of chiral lithium amide bases as enantioselective agents for proton removal appears to open up new possibilities for asymmetric synthesis. We have demonstrated that with two quite different cyclohexanone systems enantioselective deprotonation can be an effective route to chiral products in up to 88% ee. Clearly, there is still room for improvement, but even at this level of induction the cyclohexanoid products available using this method look attractive for synthesis, and particularly appropriate in the terpenoid area.

We are presently trying to extend the scope of the asymmetric deprotonation process by using other bases and ketones, and further advances will be reported separately.

Acknowlegements

We thank the SERC for a research fellowship (to R.P.C.C.) and an assistantship (to C.M.C.). We also thank the University of London Central Research Fund for an equipment grant.

Experimental

Melting points were obtained on an electrothermal hot stage apparatus. IR spectra were recorded on a Perkin Elmer 298, or 1600 series spectrometer, NMR spectra were recorded on Bruker AM 250 or WH 400 spectrometers, and mass spectra were run on a Kratos MS 902 or MS50RF instrument. Optical rotations were measured using an Optical Activity A1000 polarimeter. Elemental analyses were carried out by the University of London service at University College, London. *Cis*-2,6-dimethylcyclohexanone was obtained by column chromatography of the commercially available *cis*-*trans* mixture (Aldrich),

4-tert-butylcyclohexanone was used as supplied by Aldrich. THF was dried by refluxing over sodium/ benzophenone under a nitrogen atmosphere, petroleum ether refers to the fraction boiling 30-40°C. Acetic anhydride was freshly distilled, and Me_3SiCl was distilled from CaH and stored under nitrogen in a septum-sealed flask.

Cold reactions carried out overnight (-78°C to -40°C) were conducted using a Camlab KP 250 coldplate-stirrer.

Chiral shift experiments were conducted at ambient temperature, using ca. 0.1-0.5M solutions of substrate, and adding shift reagent portionwise (ca. 5 mg portions) until optimum peak-splitting was obtained.

Preparation of (R)-N-Benzyl-1-phenylethylamine (3a). - To a stirred solution of (R)-1-phenylethylamine (12.1 g) in MeOH (50 ml) was added methanolic HCl (6M) so as to adjust the pH to 6-7. Benzaldehyde (13.8 g) was then added, followed by $NaBH_3CN$ (4.16 g), and the mixture stoppered, and stirred at room temperature for 17 h. The MeOH was then removed under reduced pressure, before addition of water (50 ml) and KOH(s) so as to adjust the pH to > 10. The aqueous layer was saturated with NaCl(s) and then extracted with Et_2O (3 x 50 ml). The combined organic extracts were washed with 20% $FeSO_4$ (aq.) (2 x 40 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue distilled to give a colourless oil (16.27 g, 77%), b.p. 128-130°C (0.2 mm Hg). The amine was poured into hot 2M HCl (aq.) (120 ml), and on cooling the white crystals of amine hydrochloride were collected by filtration, $[\alpha]_D^{21}$ +18.1° (c = 4.0, EtOH). The free amine was recovered by stirring the salt with 2M KOH (aq) (120 ml), saturating the mixture with NaCl(s), and extracting into Et_2O (3 x 50 ml). The combined extracts were dried $MgSO_4$ and the solvent removed under reduced pressure. The residue was distilled to give the amine (3a) (13.5 g, 64%) as a colourless oil, b.p. 128-130°C (0.2 mm Hg); ν_{max} (film) 3330, 3090, 3070, 3030, 2980, 2930, 2840, 1610, 1490, 770 and 710 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.36 (3H, d, J 7 Hz), 1.60 (1H, br. s, D_2O exch.), 3.58 (1H, d, J 12.5 Hz), 3.67 (1H, d, J 12.5 Hz), 3.81 (1H, q, J 7 Hz), and 7.28 (10H, m); δ_c (63 MHz; $CDCl_3$) 24.7, 51.8, 57.6, 126.8, 127.0, 128.5, 128.6, 140.8 and 145.7; m/z 211.1 (M^+), 196.1 (M^+-CH_3), 105.1 ($PhCHCH_3^+$) and 91.1 ($C_7H_7^+$) (Found: M^+ 211.1361. $C_{15}H_{17}N$ requires M, 211.1361); $[\alpha]_D^{21}$ +54.4° (c 3.86, EtOH).

The corresponding (S) amine (4a) was prepared similarly and had the same spectral characteristics, $[\alpha]_D^{21}$ -53.6° (c 3.80, EtOH).

Preparation of (R)-N-Isopropyl-1-phenylethylamine (6a). - The same general procedure was followed as for the preparation of (3a), starting with (R)-1-phenylethylamine (12.1 g) and acetone (7.54 g). After the initial distillation of amine (6a) the HCl salt was formed as above, $[\alpha]_D^{22}$ +22.5° (c 2.03, EtOH). The free amine was then regenerated, and distilled to give (6a) (9.1 g, 56%)

as a colourless oil, b.p. 60-66°C (0.5 mm Hg) (Found: C, 80.85; H, 10.52; N, 8.59. $C_{11}H_{17}N$ requires C, 80.92; H, 10.50; N, 8.58%) ν_{max} (film) 3320, 3080, 3060, 3020, 2980, 2960, 2920, 2860, 1610, 1495, 770 and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.99 (3H, d, J 6.3 Hz), 1.02 (3H, d, J 6.3 Hz), 1.29 (1H, br. s, D_2O exch.), 1.34 (3H, d, J 6.3 Hz), 2.62 (1H, sept, J 6.3 Hz), 3.89 (1H, q, 6.3 Hz), and 7.28(5H, m); δ_C (63 MHz; $CDCl_3$) 22.2, 24.1, 24.9, 45.5, 55.1, 126.5, 126.8, 128.4 and 146.1; m/z 163.1 (M^+), 148.1 (M^+-CH_3) and 105.1 ($PhCHCH_3^+$) (Found: M^+ 163.1362. $C_{11}H_{17}N$ requires M, 163.1361); $[\alpha]_D^{22}$ +61.4° (c 2.23 $CHCl_3$).

Preparation of (R)-N-(1-Phenylethyl)bornanimine (8). - A mixture of (R)-1-phenylethylamine (32.0 g), camphor (39.5 g), and camphorsulphonic acid (0.6 g) was heated with 3A molecular sieves at 120°C for 5d. The mixture was cooled, diluted with Et_2O (50 ml) and filtered through a pad of celite. The organic solution was washed with saturated $NaHCO_3$ (aq) (2 x 40 ml) and $NaHSO_3$ (aq) (2 x 40 ml), dried ($MgSO_4$) and evaporated. Distillation of the residue gave (8) (29.7 g, 45%) as a pale yellow oil, b.p. 120-122°C (0.15 mm Hg); ν_{max} (film) 3090, 3060, 3030, 2960, 2880, 1680, 1610 and 1500 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.60 (3H, s), 0.90 (3H, s), 1.03 (3H, s), 1.42 (3H, d, J 7 Hz), 1.22 (2H, m), 1.69 (1H, m), 1.82 (3H, m), 2.24 (1H, dt, J 17, 3.8 Hz), 4.43 (1H, q, J 7 Hz), and 7.28 (m, 5H); δ_C (63 MHz; $CDCl_3$) 11.5, 19.1, 19.5, 24.6, 27.6, 32.2, 35.5, 43.9, 47.0, 53.6, 59.7, 126.2, 126.4, 128.1, 146.3 and 180.5; $[\alpha]_D^{18}$ + 36.0° (c 14, EtOH).

Reduction of (8) to give exo-(1R)-N-(1-Phenylethyl)boranamine (9a). - Imine (8) (29 g) was dissolved in MeOH (30 ml) and the pH of the resulting solution adjusted to 6-7 by the addition of 6M methanolic HCl. $NaBH_3CN$ (4.73 g) was then added and the mixture stirred at room temperature for 48 h. MeOH was removed under reduced pressure, and water (50 ml) was added followed by KOH(s) until pH > 10 was attained. The mixture was then saturated with NaCl(s) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with 20% $FeSO_4$ (aq.) (2 x 50 ml) and saturated NaCl (aq), dried ($MgSO_4$), and evaporated. Distillation of the crude amine, followed by chromatography gave (9a) (18.2 g, 62%) as a colourless oil, b.p. 122-126°C (0.1 mm Hg) (Found: C, 83.89; H, 10.78; N, 5.41. $C_{18}H_{27}N$ requires C, 83.98; H, 10.57; N, 5.44%); ν_{max} (film) 3460, 3180, 1600, 1500 and 1460 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.78 (3H, s), 0.95 (2H, m), 1.00 (3H, s), 1.18 (1H, br. s, D_2O exch.), 1.28 (3H, d, J 6.3 Hz), 1.53 (5H, m), 2.47 (1H, dd, J 7.5, 6.3 Hz, H-2), 3.75 (1H, q, J 6.3 Hz), and 7.25 (5H, m); δ_C (63 MHz; $CDCl_3$) 20.6, 24.6, 27.3, 36.9, 40.6, 45.4, 46.7, 48.7, 58.2, 65.1, 126.5, 126.9, 128.2, and 147.4; m/z 257.2 (M^+), 152.1

(M^+-CH(CH_3)Ph) and 105.1 (Found: M^+ 257.2144. $C_{18}H_{27}N$ requires M 257.21435); $[\alpha]_D^{21}$ -10.6° (c 3.23 $CHCl_3$).

The other camphor-derived amines were prepared in the same way, but without isolating the intermediate imine: (10a), colourless oil, b.p. 126°C (0.1 mm Hg) (45%) (Found: C, 83.80; H, 10.14; N, 6.41. $C_{16}H_{23}N$ requires C, 83.79; H, 10.11; N, 6.11%); ν_{max} (film) 3440, 2940, 2870, 1600, 1500, 1320, 750 and 690 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, s), 0.92 (3H, s), 1.01 (3H, s), 1.10-1.32 (3H, m), 1.52-1.80 (4H, m), 1.88 (1H, dd, J 12.5, 8.8 Hz, H-3), 3.26 (1H, dd, J 1.0, 8.8 Hz, H-2), 3.70 (1H, br. s), 6.52-6.67 (3H, m, Ph), and 7.09-7.19 (2H, m, Ph); δ_c (63 MHz; $CDCl_3$) 12.4, 20.6, 27.5, 36.9, 40.9, 45.3, 47.3, 48.9, 61.7, 112.7, 116.6, 129.3 and 148.2; m/z 229.4 (M^+), 158.4, 119.3 and 93.3 (Found: M^+ 229.183331. $C_{16}H_{23}N$ requires M, 229.183048); $[\alpha]_D^{22}$ -103.5° (c 1.56, $CHCl_3$).

(11) (38%) white solid, m.p. 117-118°C; ν_{max} ($CHCl_3$) 3440, 2940, 1600 and 1450 cm^{-1}; δ (250 MHz; $CDCl_3$) 0.86 (3H, s), 0.93 (3H, s), 1.04 (s, 3H), 1.13-1.30 (2H, m), 1.54-1.77 (4H, m), 1.89 (1H, dd, J 12.3, 8.3 Hz, H-3), 3.26 (1H, dd, J 8.3, 4.7 Hz, H-2), 3.82 (3H, s, OMe), 4.37 (1H, br. s, D_2O exch.), 6.56-6.62 (2H, m, ArH), 6.73 (1H, d, J 7.4 Hz, ArH), and 6.83 (1H, m, ArH); m/z 259 (M^+), 188, 149, 136, 123 and 95 (Found: M^+ 259.190237. $C_{17}H_{25}NO$ requires M, 259.19361); $[\alpha]_D^{21}$ -107° (c 0.73 $CHCl_3$).

(12) (58%), colourless oil; ν_{max} (film) 2960, 1600, 1490, 1450, 1370 and 1130 cm^{-1}; δ (250 MHz; $CDCl_3$) 0.62 (1H, dd, J 12.8, 4.3 Hz, H-6), 0.82 (3H, s), 0.85 (3H, s), 0.93 (3H, s), 1.11 (1H, m), 1.20-1.29 (2H, m, one D_2O exch.), 1.31 (3H, d, J 6.5 Hz), 1.50 (1H, t, J 4.5 Hz, H-4), 1.67 (1H, m), 1.80 (1H, m), 1.97 (1H, m), 2.83 (1H, ddd, J 10.3, 4.3, 2.0 Hz, H-2), 3.80 (1H, q, J 6.5 Hz), and 7.19-7.36 (5H, m); m/z 257 (M^+), 242, 186, 105 and 95 (Found: M^+ 257.2151. $C_{18}H_{27}N$ requires M, 257.21435); $[\alpha]_D^{21}$ +14.7° (c 0.43 $CHCl_3$).

Preparation of optically active 2,6-Dimethyl-2-(prop-2-enyl)cyclohexanone (15a) or (16) using chiral bases (3b), (9b), or (10b). — To a solution of amine (3a) (0.50 g) in THF (5.0 ml) under N_2 at -10°C was added a solution of ^nBuLi (1.58 ml of a 1.39 M solution in hexanes; 2.2 mmol). The resulting pinkish solution was stirred at -10°C for 1 h, and then cooled to -78°C. cis-2,6-Dimethylcyclohexanone (0.25 g) in THF (1 ml) was then added dropwise to the well-stirred solution of (3b), and the mixture maintained at -78°C for 3 h. Allyl bromide (1 ml) was then added and the mixture allowed to warm slowly to 0°C, and then maintained at that temperature until reaction was complete (TLC, 4-6 h). The mixture was then diluted with Et_2O (50 ml) and poured into 2N HCl (aq.) (50 ml). The organic layer was separated and then washed consecutively with 2N HCl (aq) (2 x 50 ml), and brine (50 ml), before drying ($MgSO_4$) and evaporation under reduced pressure.

Chromatography gave the alkylated product (15a) (0.215 g, 65%) as a mobile, colourless, sweet-smelling oil; ν_{max} (film) 3075, 1705, 1640 and 1460 cm^{-1}; δ (400 MHz; $CDCl_3$) 0.98 (3H, d, J 6.0 Hz), 1.01 (3H, s), 1.28-2.64 (9H, m), 5.02-5.06 (2H, m), and 5.60 (1H, m); $[\alpha]_D$ -25.9° (c 2.17, $CHCl_3$).

Recording the ^1H n.m.r. spectrum of this sample of (15a) in the presence of $Eu(hfc)_3$ then allowed estimation of the ee (from integration of the methyl singlet, split into two peaks at δ 1.43 and 1.47) as 25%.

Similar runs were carried out using bases (8b) and (10b). In these cases the lithium amide base was generated by addition of ^{n}BuLi to the amine in THF solution at 0°C, followed by warming to room temperature for 2 h. Addition of the ketone at -78°C and stirring at that temperature for 2 h was followed by slow warming to -40°C (coldplate overnight) and quench with excess allyl bromide (-40 to 0°C) as before.

Using base (9b) the obtained (16) (55%), $[\alpha]_D^{21}$ +94.5° was shown to have an ee of 64%. Likewise with base (10b) the ketone (15a) (57%), $[\alpha]_D^{21}$ -96.5° had an estimated ee of 68%.

Preparation of optically active 1-Acetyloxy-2,6-dimethylcyclohex-1-ene (17a) or (17b) using chiral bases. — To a solution of amine (9a) (0.668 g) in THF (4 ml) under N_2 at -10°C was added a solution of ^{n}BuLi (1.5 ml of a 1.6 M solution in hexanes; 2.4 mmol). After 30 min. the cooling bath was removed and the mixture stirred at room temperature for 2 h before cooling to -78°C. cis-2,6-Dimethylcyclohexanone (0.252 g) in THF (1 ml) was then added dropwise and the mixture allowed to warm very slowly to -40°C overnight (coldplate). The mixture was then quenched by addition of Ac_2O (1.5 ml) and stirred for a further 40 min. before dilution with Et_2O (50 ml) and pouring into 2N HCl (aq.) (50 ml). The organic layer was washed with 2N HCl (2 x 50 ml), brine (50 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue gave (17b) (0.218 g, 65%) as a colourless oil; ν_{max} (film) 2930, 2870, 1760 and 1715 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.97 (3H, d, J 7 Hz), 1.39 (m, 1H), 1.51 (3H, br. s), 1.55-1.75 (2H, m), 1.87 (1H, m), 2.04 (2H, m), 2.15 (3H, s), and 2.41 (1H, m); δ_C (63 MHz; $CDCl_3$) 16.4, 18.3, 20.2, 20.7, 30.7, 31.6, 31.8, 120.5, 145.6 and 169.1; m/z 168.1 (M^+), 126.1, 111.1, 98.1 and 84.1 (Found; M^+ 168.1150. $C_{10}H_{16}O_2$ requires M, 168.11503); $[\alpha]_D^{19}$ -40.2° (c 4.0, $CHCl_3$).

Examination of the ^1H n.m.r. spectrum of this sample of (17b) in the presence of $Eu(hfc)_3$ allowed estimation of the ee (splitting of the $CO\underline{CH}_3$ signal) as 65%.

Similar runs using other chiral bases gave the same enol acetate product with the following optical data: base (3b), (17a) (75%), $[\alpha]_D^{20}$ +13.0° (c 5.6, $CHCl_3$), 29% ee; base (6b), (17b) (71%), $[\alpha]_D^{19}$ -21.2° (c 4.0, $CHCl_3$), 32% ee; base (1b), (17a) (71%), $[\alpha]_D^{19}$ +28.9° (c 2.3 $CHCl_3$), 43% ee;

base (10b), (17a) (68%), $[\alpha]_D$ +50.3° (c 4.3 $CHCl_3$), 74% ee; base (14), (17a) (28%), $[\alpha]_D^{20}$ +5.6° (c 1.0 $CHCl_3$), 8% ee; base (12), (17a) (76%), $[\alpha]_D^{18}$ +3.7° (c 2.0 $CHCl_3$), 5% ee; base (13), (17a) (70%), $[\alpha]_D^{20}$ +10.0° (c 2.0 $CHCl_3$), 14% ee.

Preparation of optically active 2,6-Dimethyl-1-trimethylsilyloxycyclohex-1-ene (18a) or (18b) using chiral bases. - Deprotonation of cis-2,6-dimethylcyclohexanone (1.26 g) was carried out using base (9b) exactly as described above in the preparation of (17b). The resulting enolate solution at -40°C was recooled to -78°C and Me_3SiCl (4 ml), and Et_3N (4 ml) were added. After a further 1 h at -78°C the solution was poured into saturated NH_4Cl (aq.) (30 ml) and the product extracted into petroleum ether (2 x 30 ml). The combined organic extracts were washed with saturated NH_4Cl (aq.) (3 x 40 ml), and brine (3 x 40 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography of the residue on florisil gave (18b) (1.3 g, 66%) as a colourless oil; ν_{max} (film) 2920, 2860 and 1675 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.18 (9H, s), 1.05 (3H, d, J 7 Hz), 1.25-1.52 (2H, m), 1.56 (3H, s), 1.57-1.69 (1H, m), 1.76 (1H, m), 1.94 (2H, m), and 2.13 (1H, m); m/z 198.1 (M^+), 183.1, 167.5 and 109.1 (Found: M^+ 198.1435. $C_{11}H_{22}OSi$ requires M, 198.14399; $[\alpha]_D^{23}$ -20° (c 0.42, CH_2Cl_2). Portions of this product were used in the following reactions.

Preparation of (2S,6S)-2,6-Dimethyl-2-hydroxycyclohexanone (19).[25] — A solution of (18b) (0.5 g, $[\alpha]_D^{23}$ -20°) in petroleum ether (10 ml) was cooled to -10°C, and mCPBA (0.473 g) was added in portions with stirring. After 1 h the reaction was complete (TLC) and the precipitated m-chlorobenzoic acid was filtered off. The reaction mixture was again cooled to -10°C and a solution of $^nBu_4NF$ in THF (1 ml of a 1M solution) was added. The stirred reaction mixture was then allowed to warm to room temperature overnight. Et_2O (25 ml) was then added and the mixture poured into saturated $NaHCO_3$ (aq.) (20 ml). The organic layer was separated and then washed consecutively with 2N HCl (aq.) (20 ml) and saturated $NaHCO_3$ (aq.) (20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Flash chromatography of the residue gave (19) (0.22 g, 61%) as a colourless oil; ν_{max} (film) 3450, 2920, 2860 and 1710 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.03 (3H, d, J 6.3 Hz), 1.30 (s, 3H), 1.38 (1H, m), 1.52-1.65 (2H, m), 1.92-2.07 (3H, m), 2.56 (1H, br. s), and 3.08 (1H, sept, J 6.3 Hz); δ_C (63 MHz; $CDCl_3$) 14.9, 20.3, 24.6, 36.2, 40.8, 41.6, 75.8 and 214.6; m/z 142.1 (M^+), 114.1, 84.1 and 71.1 (Found: M^+ 142.0994. $C_8H_{14}O_2$ requires M, 142.09938); $[\alpha]_D^{21}$ +25.5° (c 2.0 CH_2Cl_2).

The Mosher's ester derivative was prepared by refluxing a solution of (19) (0.04 g, $[\alpha]_D$ -22.9°) and (+)-methoxyphenyltrifluoromethylacetylchloride

(MTPACl) (0.17 g) and 4-dimethylaminopyridine (DMAP) (0.082 g) in CH_2Cl_2 for 17 h. The resulting mixture was cooled and water (1 ml) added followed by Et_2O (20 ml). The organic layer was washed with 2N HCl (aq.) (10 ml), saturated $NaHCO_3$ (10 ml), and water (10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the ^1H n.m.r. spectrum of the crude residue was recorded. The ratio of the quartets at δ 3.57 and 3.53 (OMe, J 1.25 Hz) gave an estimate of the de of 56%. The crude residue was then purified by chromatography to give the MTPA ester of (19) (0.071 g, 97%). Examination of the ^1H n.m.r. of the purified material again gave a de of 56%; δ (250 MHz; $CDCl_3$) 1.03 (3H, d, J 6.3 Hz), 1.18-1.38 (2H, m), 1.53 (3H, s), 1.58-1.85 (2H, m), 1.89-2.25 (1H, m), 2.30-2.44 (1H, m), 2.61 (1H, m), 3.57 and 3.53 (3H, q, J 1.25 Hz), 7.34-1.47 (3H, m), and 7.54-7.65 (2H, m).

Preparation of (2S,6S)-2-Bromo-2,6-dimethylcyclohexanone (20). – A solution of (18b) (0.530 g, $[\alpha]_D$ -20°) in CH_2Cl_2 (7 ml) was cooled to 0°C and N-bromosuccinimide (0.528 g) was added with stirring. After 40 min CH_2Cl_2 (25 ml) was added and the organic layer was washed with $Na_2S_2O_3$ (3 x 30 ml), saturated NaCl (aq.) (2 x 30 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was subjected to column chromatography to yield (20) (0.22 g, 40%) as a colourless oil; ν_{max} (film) 2920, 2860 and 1715 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, d, J 6.3 Hz), 1.32 (1H, m), 1.68-1.80 (2H, m), 1.82 (3H, s), 2.00-2.20 (2H, m), 2.39 (1H, m), and 3.41 (1H, sept, 6.3 Hz); δ_C (63 MHz; $CDCl_3$) 14.8, 22.5, 28.5, 36.1, 39.7, 44.4, 65.9 and 206.9; m/z 204.0 (M^+), 125.1, 97.1, 71.1 and 55.0 (Found: M^+ 204.0147. $C_8H_{13}OBr$ requires M, 204.01498); $[\alpha]_D^{24}$ +82° (c 1.1, CH_2Cl_2). Examination of the ^1H n.m.r. spectrum of this sample of (20) in the presence of $Eu(hfc)_3$ allowed estimation of the ee (splitting of the CH_3 doublet into two doublets centred at δ 1.42 and 1.34) as 65%.

Preparation of (2R,6S)-2-Acetyl-2,6-dimethylcyclohexanone (21).[26] – A stirred solution of $SnCl_4$ (0.574 g) in CH_2Cl_2 (4.0 ml) under N_2 was cooled to -10°C, and CH_3COCl (0.171 g) was added. After 5 min a solution of (18b) (0.40 g, $[\alpha]_D$ -20°) in CH_2Cl_2 (3 ml) was added dropwise. After 1.5 h water (10 ml) was added and the product extracted into CH_2Cl_2 (2 x 15 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (aq.) (2 x 25 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography of the residue gave (21) (0.10 g, 30%) as a colourless oil; ν_{max} (film) 2940, 2875 and 1705 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.04 (3H, d, J 6.3 Hz), 1.40 (3H, s), 1.40-1.56 (1H, m), 1.65-1.75 (1H, m), 1.80-1.91 (2H, m), 2.03-2.14 (1H, m), 2.17 (3H, s), 2.19-2.32 (1H, m), and 2.65 (1H, sept, J 6.3 Hz); δ_C (63 MHz; $CDCl_3$) 14.9, 20.2, 20.5, 27.3, 35.2, 35.4, 41.9, 62.2, 208.4 and

214.1; m/e 168.1 (M^+), 126.1, 111.1 and 98.1 (Found; M^+ 168.1150. $C_{10}H_{16}O_2$ requires M, 168.11503); $[\alpha]_D^{24}$ +30.9° (c 1.6 CH_2Cl_2). We were unable to determine the ee of (21) using chiral shift reagents in ^1H n.m.r. experiments.

Preparation of (S)-2,6-Dimethylcyclohex-2-en-1-one (23). — To a solution of (18b) (0.30 g, $[\alpha]_D$ -20°) in CH_2Cl_2 (3.0 ml) under N_2 at -78°C was added a solution of PhSeCl (0.35 g) in CH_2Cl_2 (3.0 ml), dropwise, with stirring. After 10 min the mixture was diluted with CH_2Cl_2 (10 ml) and washed with saturated $NaHCO_3$ (aq.) (25 ml), and brine (25 ml), dried ($MgSO_4$), and evaporated. The crude β-ketoselenide (22) was dissolved in CH_2Cl_2 (3.0 ml), cooled to -40°C, and 16% H_2O_2 (aq) (0.4 ml) added. The reaction was then warmed to room temperature (1.5 h), and the mixture worked up as before. Chromatography of the residue gave (23) (0.14 g, 78%) as a colourless oil; ν_{max} (film) 3020, 2925, 2860 and 1675 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.14 (3H, d, J 6.3 Hz), 1.62-1.80 (1H, m), 1.76 (3H, m), 2.05 (1H, m), 2.35 (3H, m), and 6.68 (1H, m); δ_C (63 MHz; $CDCl_3$), 15.3, 16.2, 25.3, 31.3, 41.6, 135.1, 144.5 and 202.5; m/z 124.1 (M^+) and 96.0 (Found: M^+ 124.0864. $C_8H_{12}O$ requires M, 124.08881); $[\alpha]_D^{20}$ -58.2° (c 0.77 CH_3OH) (lit. $[\alpha]_D^{25}$ -82° (c 0.06 CH_3OH)).

Examination of the ^1H n.m.r. spectrum of (23) in the presence of Eu(tfc)$_3$ allowed estimation of the ee (splitting of the Me doublet into two doublets centred at δ 1.32 and 1.34) as 68%.

Preparation of optically active 4-tert-Butyl-1-trimethylsilyloxycyclohex-1-ene (25) using chiral bases. — Chiral base (6b) was prepared under a nitrogen atmosphere by the addition of n-butyllithium (0.9 ml, 2.4 mmol) to chiral amine (6a) (0.424 g) at -78°C in THF (40 ml). After 5 min the mixture was allowed to warm to room temperature and then recooled to -78°C. Me_3SiCl (1.3 ml) was added and after 2 min 4-tert-butylcyclohexanone (0.308 g) was added dropwise in THF (10 ml) over a period of 5 min. The mixture was stirred for a further 10 min at -78°C. Triethylamine (4 ml) and saturated $NaHCO_3$ (aq.) (10 ml) were added and the mixture was extracted with petroleum spirit (2 x 40 ml) and the organic layer was washed with saturated NH_4Cl (aq.) (2 x 20 ml), saturated $NaHCO_3$ (aq.) (2 x 20 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was subjected to chromatography, and then distilled to give (25) (0.37 g, 82%) as a colourless oil, b.p. 66-67°C (0.44 mm Hg); ν_{max} 3040, 2960, 2870 and 1675 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.18 (9H, s), 0.87 (9H, s), 1.12-1.34 (2H, m), 1.73-1.88 (2H, m), 1.95-2.25 (3H, m), and 4.84 (1H, m); δ_C (63 MHz; $CDCl_3$) 0.44, 24.5, 25.2, 27.5, 31.1, 32.2, 44.1, 104.1 and 150.4; m/z 226.2 (M^+), 211.2 (M^+-Me), 169.1, 142.1 and 127.1 (Found: M^+ 226.1752. $C_{13}H_{26}OSi$ requires M, 226.17529); $[\alpha]_D^{21}$ -44.9° (c 1.5 $CHCl_3$).

Similar experiments using other chiral bases gave the same silyl enol ether (25), with the following optical data: base (1b) (73%), $[\alpha]_D^{20}$ -54.4° (c 1.7 $CHCl_3$), $[\alpha]_{365}^{21}$-171.5° (c 1.7 $CHCl_3$); base (3b) (71%), $[\alpha]_D^{21}$ -42.9° (c 1.5 $CHCl_3$), $[\alpha]_{365}^{21}$ -133.9° (c 1.5 $CHCl_3$); base (9b) (80%), $[\alpha]_D^{21}$ -16.1° (c 1.5 $CHCl_3$); base (10b) (75%), $[\alpha]_D^{21}$ -23.5° (c 1.52 $CHCl_3$), $[\alpha]_{365}$ -67.9° (c 1.52 $CHCl_3$).

The above experiments were repeated using chiral bases (1b) and (6b) at the lower temperature of -90°C (bath temp.). Silyl enol ether (25) was produced in the yield shown below, and with the indicated optical rotation: base (1b) (66%), $[\alpha]_D^{21}$ -69.2° (c 1.5 $CHCl_3$), $[\alpha]_D^{21}$ -73.3 (c 1.56 PhH), $[\alpha]_{365}^{21}$ -218.6° (c 1.5 $CHCl_3$); base (6b) (81%), $[\alpha]_D^{21}$ -51.0° (c 1.2 $CHCl_3$).

Preparation of (S)-4-tert-Butylcyclohex-2-en-1-one (26).-

(a) Using the method of Tsuji.[21]

To a solution of $Pd(OAc)_2$ (0.045 g) in refluxing CH_3CN (3.0 ml) under N_2 was added a mixture of (S)-4-tert-butyl-1-trimethylsilyloxycyclohex-1-ene (0.43 g) ($[\alpha]_D$ -36.2°) and diallyl carbonate (0.568 g) in CH_3CN (2.0 ml). The solution was refluxed for 1 h and then cooled, diluted with Et_2O (40 ml), washed with saturated NaCl (aq.) (3 x 30 ml) and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue chromatographed to give enone (26) (0.27 g, 86%) as a colourless oil; ν_{max} (film) 3040, 2960, 2820, and 1680 cm^{-1}; δ (250 MHz; $CDCl_3$) 0.98 (9H, s), 1.75 (1H, m), 2.05-2.41 (3H, m), 2.53 (1H, m), 6.04 (1H, ddd, J 10.0, 2.5, 1.3 Hz), and 7.03 (1H, dt, J 10.0, 2.5 Hz); m/z 152.1 (M^+), 137.1, 96,0 and 57.1 (Found: M^+ 152.1204. $C_{10}H_{16}O$ requires M, 152.12012); $[\alpha]_D^{22}$ -28.1° (c 1.56 $CHCl_3$).

(b) via reaction of (25) with PhSeCl.

To a solution of (25) (0.30 g, $[\alpha]_D$ -42.9°) in CH_2Cl_2 (3.0 ml) at -78°C, under N_2, was added a solution of PhSeCl (0.35 g) in CH_2Cl_2 (3.0 ml). After 10 min the mixture was diluted with more CH_2Cl_2 (10 ml) and then washed with saturated $NaHCO_3$ (aq) (2 x 10 ml) and brine (20 ml), and dried ($MgSO_4$). The resulting solution of crude selenide was cooled to -78°C, and ozone was bubbled through until a permanent greenish-blue colouration was obtained (2 h). The solution was allowed to warm to room temperature and Et_3N (4.0 ml) was added. The solution was then poured into saturated $NaHCO_3$ (aq.) (25 ml), and the organic layer separated and washed with brine (2 x 20 ml) and dried ($MgSO_4$). The solvent was then removed under reduced pressure, and the residue chromatographed, and then distilled (Kugelruhr; oven temp. 130°C at 0.5 mm Hg) to give enone (26) (0.09 g, 21%), with the same spectral characteristics as before: $[\alpha]_D^{17}$ -35.8° (c 1.03, $CHCl_3$).

Preparation of (3S,4S)-3-Methyl-4-tert-butylcyclohexanone (27). — A slurry of CuBr.SMe_2 (0.322 g) in sodium-dried Et_2O (3.0 ml) under N_2 was cooled to -20°C, and MeLi (2.8 ml of a 1.4 M solution in Et_2O) was then added with stirring. After 20 min the resulting clear solution was cooled to -78°C and (4S)-4-tert-butylcyclohex-2-en-1-one (0.18 g, $[\alpha]_D^{22}$ -28.1°) was added in Et_2O (1.0 ml). After 3 h the mixture was diluted with Et_2O (25 ml), and then washed with saturated NH_4Cl (aq.) (3 x 30 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was chromatographed to give (27) (0.136 g, 65%) as a colourless oil; ν_{max} (film) 2960, 2870 and 1725 cm^{-1}; δ (250 MHz; $CDCl_3$) 0.93 (9H, s), 0.97 (3H, d, J 7.5 Hz), 1.51-1.68 (1H, m), 1.86 (1H, m), 2.10 (3H, m), and 2.35-2.56 (2H, m); m/z 168.2 (M^+), 153.1, 112.1 and 57.1 (Found: M^+ 168.1517. $C_{11}H_{20}O$ requires M, 168.15141); $[\alpha]_D^{20}$ -111.5° (c 1.1 $CHCl_3$).

A different sample of enone (26) ($[\alpha]_D^{17}$ -35.8°) was reacted in the same way, to give ketone (56%) with the same spectral characteristics as before: $[\alpha]_D^{20}$ -126.8° (c 1.1 $CHCl_3$).

Preparation of (2S,4S)-2-Hydroxy-4-tert-butylcyclohexanone (28a). — A solution of silyl enol ether (25) (0.255 g, $[\alpha]_D^{21}$ -69.2°) in CH_2Cl_2 (5.0 ml) was cooled to -20°C and m-chloroperbenzoic acid (0.224 g) was added in portions with stirring. After 1.5 h the precipitated acid was filtered off and washed with petroleum spirit (10 ml). After removal of the solvent the residue was dissolved in CH_2Cl_2 (5.0 ml) and $^nBu_4NF$ in THF (1.5 ml of a 1M solution) was added at room temperature, with stirring. After 1 h the mixture was diluted with CH_2Cl_2 (25 ml) and washed with saturated $NaHCO_3$ (aq.) (50 ml), 2N HCl (aq.) (2 x 30 ml), and saturated $NaHCO_3$ (aq.) (30 ml), and dried ($MgSO_4$). The residue was chromatographed to give (28a) (0.08 g, 40%), as a white solid, m.p. 61-62°C; ν_{max} (KBr disc) 3412, 2944, 2840 and 1705 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.93 (9H, s), 1.23-1.71 (3H, m), 2.06-2.18 (1H, m), 2.31-2.60 (3H, m), 3.58 (1H, br. s), and 4.14 (1H, dd, J 12.5, 7.5 Hz); δ_C (63 MHz, $CDCl_3$) 27.7, 28.6, 32.5, 38.0, 38.5, 45.3, 75.0 and 211.7; m/z 170.1 (M^+), 137.1, 126.1, 114.1, 96.1 and 85.0 (Found: M^+ 170.1307. $C_{10}H_{18}O_2$ requires M, 170.13068); $[\alpha]_D^{21}$ -44.8° (c 0.58 $CHCl_3$). The other minor diastereomeric alcohol (28b) could not be obtained pure.

The Mosher's ester derivative of (28a) was prepared by refluxing a solution of (28a) (0.0217 g, $[\alpha]_D$ -44.8°) and MTPACl (0.079 g), and DMAP (0.038 g) in CH_2Cl_2 (5.0 ml) for 1.5 h. After the usual workup the ^1H n.m.r. spectrum of the crude residue was recorded. The ratio of the quartets at δ 3.69 and 3.58 (OMe, J 1.25 Hz) gave an estimate of the de at 88%. The crude residue was then purified by chromatography to give the MTPA ester (29) (0.048 g, 97%). The de of this product was 87% as judged from the ^1H n.m.r.

spectrum; δ (250 MHz; $CDCl_3$) 0.92 and 0.96 (9H, s), 1.36-1.55 (1H, m), 1.60-1.82 (2H, m), 2.07-2.18 (1H, m), 2.34-2.59 (3H, m), 3.58 and 3.69 (3H, q, J 1.25 Hz), 5.36 (1H, m), 7.43 (3H, m), and 7.68 (2H, m).

Preparation of (S)-3-tert-Butylhexan-1,6-dioic acid (30). — Ozone was bubbled through a stirred mixture of (25) (0.500 g, $[\alpha]_D$ -48.8° (c 1.66 $CHCl_3$)) and methanol (3 ml) for 3 h from -40 to -10°C. The methanol was then blown off with N_2 at room temperature. The viscous clear oil obtained was cooled to -40°C and a mixture of hydrogen peroxide (30%, 1 ml) and formic acid (90%, 3 ml) was added with stirring. The mixture was allowed to warm to -10°C over 2 h and was then refluxed for 40 min. The solvent was removed under reduced pressure and the residue was purified using flash chromatography on silica gel to furnish 0.270 g (60%) of (30) as a white solid, m.p.112-114°C; ν_{max} (KBr disc) 3000-2500 (br.) and 1700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.92 (9H, s), 1.43 (1H, hept, J 7.5 Hz), 1.75 (1H, sept, J 3.8 Hz), 1.95 (1H, m), 2.10 (1H, dd, J 15.3, 7.5 Hz), 2.35-2.57 (3H, m), and 10.4 (2H, br.s, D_2O exch.); δ_c (63 MHz, $CDCl_3$) 26.0, 27.3, 33.5, 33.8, 36.0, 44.4, 180.1, and 180.9; $[\alpha]_D$ +11.4° (c 1.03 acetone).

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We also note that at values of c lower than about c = 0.8 there is a distinct concentration dependence of the $[\alpha]_D$ values.

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